NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 438

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZETHONIUM CHLORIDE

(CAS NO. 121-54-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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P.O. Box 12233
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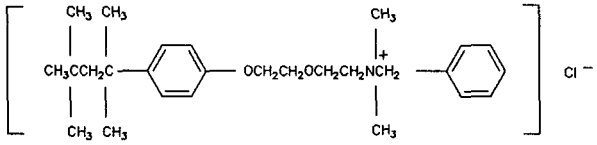

BENZETHONIUM CHLORIDE

CAS No. 121-54-0

Chemical Formula: $C_{27}H_{42}NO_2 \cdot Cl$ Molecular Weight: 448.1

Synonyms: Benzyldimethyl-*p*-(1,1,3,3-tetramethylbutyl) phenoxyethoxy-ethylammonium chloride; diisobutylphenoxyethoxy-ethyldimethyl benzyl ammonium chloride; *p*-tert-octylphenoxyethoxyethyldimethylbenzyl ammonium chloride

Trade names: Anti-germ 77, Antiseptol, BZT, Diapp, Disilyn, Hyamine, Hyamine 1622, Phemeride, Phemithyn, Polymine D, Quatrachlor, Solamine

Benzethonium chloride is used primarily in cosmetics for its antimicrobial and cationic surfactant properties. Benzethonium chloride was nominated by the National Cancer Institute to the NTP for study from a class study of chemicals used as biocides. The chemical was selected based on a suspicion of carcinogenicity and its known widespread human exposure. Male and female F344/N rats and B6C3F$_1$ mice were topically administered benzethonium chloride (greater than 98% pure) for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

16-Day Study in Rats

Groups of five male and five female F344/N rats were topically administered 0, 6.3, 12.5, 25, 50, or 100 mg benzethonium chloride/kg body weight. Rats were administered a total of 12 doses in a fixed volume of 250 μL ethanol. All rats survived to the end of the study. The final mean body weights and body weight gains of rats administered 50 or 100 mg benzethonium chloride/kg body weight were significantly less than those of the controls. Clinical findings at necropsy included thickening or hardening of the skin at the site of application in all rats administered 50 or 100 mg/kg and in 25 mg/kg males. Lesions at the site of application appeared crusty or red-grey in color. Epithelial hyperplasia with or without inflammation occurred at the site of application in all groups of males and females administered benzethonium chloride.

16-Day Study in Mice

Groups of five male and five female B6C3F$_1$ mice were topically administered 0, 6.3, 12.5, 25, 50, or 100 mg benzethonium chloride/kg body weight. Mice were administered a total of 12 doses in a fixed volume of 100 μL ethanol. One 100 mg/kg male mouse died on day 4 of the study. Final mean body weights of all groups of males and females were similar to those of the controls. Clinical findings included mild irritation at the site of application in 50 and 100 mg/kg males and females and in 25 mg/kg males. Epithelial hyperplasia with or without inflammation occurred at the site of application in all groups of males and females administered benzethonium chloride.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were topically administered 0, 1.56, 3.13, 6.25, 12.5, or 25 mg benzethonium chloride/kg body weight, 5 days per week for 13 weeks. Doses were administered in ethanol at a volume not exceeding 300 μL. All rats survived to the end of the study. The final mean body weight and body weight gain of 25 mg/kg males were significantly lower than those of the controls. The final mean body weights of all other groups of males and of all groups of females were similar to those of the controls. Clinical findings included irritation at the site of application in groups administered 3.13 mg/kg or greater. There were no differences in absolute or relative organ weights considered to be related to chemical administration. Epithelial hyperplasia was observed at the site of application in all groups of males and females administered benzethonium chloride. Additionally, inflammation and ulceration were observed at the site of application in males and females administered 3.13 mg/kg or greater. Based on the lesions observed in the 13-week study, benzethonium chloride dose levels selected for the 2-year dermal study in male and female rats were 0.15, 0.5, and 1.5 mg/kg.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were topically administered 0, 1.56, 3.13, 6.25, 12.5, or 25 mg benzethonium chloride/kg body weight, 5 days per week for 13 weeks. Doses were administered in ethanol at a volume not exceeding 100 μL. All mice survived to the end of the study. The final mean body weights of all dosed groups of males and females were similar to those of the controls; the mean body weight gain of 25 mg/kg males was significantly less than that of the controls. Males administered 6.25, 12.5, or 25 mg/kg developed irritation, thickening of the skin, scales, and/or discoloration at the site of application, as did female mice administered 12.5 or 25 mg/kg. Increased incidences of epithelial hyperplasia and inflammation were observed at the site of application in all groups of males and females administered benzethonium chloride. Based on the lesions observed in the 13-week study, benzethonium chloride dose levels selected for the 2-year dermal study in mice were 0.15, 0.5, and 1.5 mg/kg.

2-YEAR STUDY IN RATS

Groups of 60 male and 60 female F344/N rats were topically administered 0, 0.15, 0.5, or 1.5 mg benzethonium chloride/kg body weight 5 days per week for 103 weeks. Doses were administered in ethanol, and dose volumes were adjusted weekly according to the average body weights of the groups. As many as nine rats per group were evaluated after 15 months of chemical administration.

Survival, Body Weights, and Clinical Findings

Survival of dosed rats was similar to that of the controls throughout the study. Mean body weights of all dosed groups of males and females were similar to those of the controls throughout the study. Reddening of the skin was observed at the site of application in all dosed groups of males and females. There were no other clinical findings considered to be related to chemical administration.

Pathology Findings

There were no increased incidences of neoplasms in dosed male or female rats that were attributed directly to the administration of benzethonium chloride. Increased incidences of epithelial hyperplasia, sebaceous gland hyperplasia, and ulcers were observed at the site of application in dosed females. The incidence of epithelial hyperplasia was increased in 0.5 and 1.5 mg/kg males.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female B6C3F$_1$ mice were topically administered 0, 0.15, 0.5, or 1.5 mg benzethonium chloride/kg body weight 5 days per week for 103 weeks. Doses were administered in ethanol, and dose volumes were adjusted weekly according to the average body weights of the groups. As many as 10 mice per group were evaluated after 15 months of chemical administration.

Survival, Body Weights, and Clinical Findings

Survival of dosed mice was similar to that of the controls throughout the study. Mean body weights of all dosed groups of males and females were similar to those of the controls throughout the study. Reddening of the skin was observed at the site of

application in all dosed groups of males and in 0.15 mg/kg females. There were no other clinical findings attributed to chemical administration.

Pathology Findings

There were no increased incidences of neoplasms in dosed males or females that were related to administration of benzethonium chloride. Increased incidences of epithelial hyperplasia were observed at the site of application in dosed males and females.

GENETIC TOXICOLOGY

Benzethonium chloride was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 and did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. All tests were conducted with and without S9 metabolic activation enzymes.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of benzethonium chloride in male or female F344/N rats receiving 0.15, 0.5, or 1.5 mg/kg. There was *no evidence of carcinogenic activity* in male or female $B6C3F_1$ mice receiving 0.15, 0.5, or 1.5 mg/kg.

Exposure of rats and mice to benzethonium chloride by dermal application in ethanol for 2 years resulted in epithelial hyperplasia in male and female rats and mice and sebaceous gland hyperplasia and ulcers in female rats at the site of application.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Benzethonium Chloride

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 0.15, 0.5, or 1.5 mg/kg in not more than 296 µL of acetone	0, 0.15, 0.5, or 1.5 mg/kg in not more than 317 µL of acetone	0, 0.15, 0.5, or 1.5 mg/kg in not more than 131 µL of acetone	0, 0.15, 0.5, or 1.5 mg/kg in not more than 131 µL of acetone
Body weights	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls
2-Year survival rates	15/52, 11/52, 9/55, 16/56	24/51, 33/53, 26/51, 24/53	43/50, 38/50, 42/50, 39/50	38/52, 34/53, 31/48, 34/54
Nonneoplastic effects	Skin (site of application): epithelial hyperplasia (1/52, 0/52, 4/55, 12/56)	Skin (site of application): epithelial hyperplasia (2/51, 2/53, 6/51, 32/53); sebaceous gland hyperplasia (1/51, 2/53, 6/51, 30/53); ulcer (0/51, 1/53, 3/51, 19/53)	Skin (site of application): epithelial hyperplasia (2/50, 7/50, 16/50, 23/50)	Skin (site of application): epithelial hyperplasia (3/52, 7/53, 6/48, 22/54)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on benzethonium chloride on June 21, 1994, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 21, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of benzethonium chloride received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

Dr. J.R. Bucher, NIEHS, introduced the toxicology and carcinogenesis studies of benzethonium chloride by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in rats and mice. The proposed conclusions were *no evidence of carcinogenic activity* of benzethonium chloride in male and female F344/N rats and in male and female B6C3F$_1$ mice. Dermal exposure of rats and mice to benzethonium chloride in ethanol for 2 years resulted in epithelial hyperplasia in male and female rats and mice and sebaceous gland hyperplasia and ulcers in female rats at the site of application.

Dr. Bailey, a principal reviewer, agreed with the proposed conclusions and believed the dose levels selected were adequate to evaluate the carcinogenic potential of the chemical in rats and mice.

Dr. Vodicnik, the second principal reviewer, also agreed with the proposed conclusions. She questioned part of the rationale for study of the chemical (i.e., "suspicion of carcinogenicity"). She said that the statement was based on results of a dated, isolated study in which commercial grade benzethonium chloride was administered subcutaneously to rats, and noted that the localized sarcomas observed in the study were typical of those resulting from repeated irritation. Dr. Vodicnik said sufficient rationale for study was the widespread human exposure and lack of adequate testing. Dr. Bucher noted that some human carcinogens (e.g., nickel compounds) are very difficult to show as being carcinogenic in animal studies by other than an injection route. He thought it an appropriate response by the NTP to do this study by the dermal route to clarify whether there was, in fact, any suspicion of carcinogenicity. Dr. Vodicnik added that part of her concern had to do with the lack of characterization of the test material and impurities in the earlier study.

Dr. Reddy, the third principal reviewer, also agreed with the proposed conclusions, but believed the high dose administered to male rats and mice in the 2-year studies could have been greater. Dr. Bucher agreed. Dr. Reddy asked whether it would be appropriate to modify future dermal study protocols to examine the potential promoting effect of compounds such as benzethonium chloride. Dr. Bucher asked the subcommittee to comment on the value of promotion studies.

Dr. Ward said that he agreed with the rationale for study, adding that the results of the studies on benzethonium chloride provide more evidence that chronic irritation alone does not cause neoplasms. Dr. Ryan asked for clarification of a statement that sebaceous gland carcinomas in treated male rats were consistent with the spectrum of neoplasms found in adjacent control skin from treated and untreated animals. Dr. Bucher said that these lesions in treated animals were similar to those observed in control animals, suggesting that these neoplasms were not associated with chemical exposure. Dr. Klaassen asked why there was a tenfold difference between the lowest and highest doses administered in this study, adding that the difference is generally fourfold. Dr. D.S. Marsman, NIEHS, said that between the 16-day and 13-week studies, there appeared to be more lesions developing at lower dose levels; thus, a wider dose range in the 2-year studies could have allowed for continuance of this observation. Dr. Miller commented that in view of the widespread human exposure in skin products, it would be useful to relate the doses applied to typical concentrations in consumer products. Dr. Bucher agreed.

Dr. Bailey moved that the Technical Report on benzethonium chloride be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Vodicnik seconded the motion, which was accepted unanimously with 11 votes.